## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The influence of information provided prior to switching from Humira to biosimilar adalimumab on UK patients' satisfaction: a cross sectional survey by patient organisations. |
| **AUTHORS** | Kaneko, Kayoko; Prieto-Alhambra, Daniel; Jacklin, Clare; Bosworth, Ailsa; Dickinson, Sally; Berry, Sarah; McAteer, Helen; Taylor, Peter |

## VERSION 1 – REVIEW

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| **REVIEWER** | Cohen, Stanley<br>Metroplex Clinical Research Center |
| **REVIEW RETURNED** | 09-Jun-2021 |

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| **GENERAL COMMENTS** | Interesting reusults from the survey which confirm previous observations in other population cohorts. Well written with clear presentation of the results |

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| **REVIEWER** | Gardarsdottir, Helga<br>Utrecht University Utrecht Institute for Pharmaceutical Sciences, Division Pharmacoepidemiology and Clinical Pharmacology |
| **REVIEW RETURNED** | 16-Jun-2021 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review the manuscript entitled "The influence of information provided prior to switching from Humira to biosimilar adalimumab on UK patients' satisfaction: a cross sectional survey by patient organisations.", which I read with great interest. The manuscript presents a well-conducted study with interesting results. However, I do have some comments on parts of the manuscript<br>Major comments:<br>Introduction<br>Several statements in the introduction are not referenced or unclear, some examples include;<br>- Page 1, line 28-46 spendings on adalimumab. Please add reference to support your claims/theories<br>- Page 8, line 52-53: reference to studies on perception of patients that have not switched, what are these? Would be useful to include to show relevance.<br>- Page 9, line 6-9: The authors state that switching may cause anxiety and suspicion, please reference this statement.<br><br>Method<br>- The development of the survey is not described in any detail. What steps were taken during the development? How did the authors go about validating the questions asked? |

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| | - How did the authors analyse the comments and answers to the fully open questions reported?<br>- When assessing participants perception on efficacy, the authors excluded all patients that reported “the same”. This is a major concern and seems strange as one would assume that switching to a similar product should not necessarily improve perception on efficacy, but to sustain or improve (at least not lead to worse perception). The results show that a large part of the population does opt for this answer, and it would also be expected.<br><br>Results<br>- Where are the results from the free comments and open questions presented? (see also my comment on the method section)<br>- Information on if patients were satisfied with Humira before switching are missing. Was this measured? As the biosimilar is similar, patients who were not satisfied with Humira before switching might be less likely to feel satisfied with the biosimilar (Table 2, question 4).<br>- On page 14, line 24-30 the results show that patients reported lack of training and majority reported that they did not receive an option to decline or delay switching to a biosimilar. Where these elements obligatory to offer based on the NHS recommendation? In addition, for some questions the answer can represent two types of views. Such as when it regards the option to decline - was the question asked if they wanted to switch? Or did they object to switching but this was not offered as an option? The latter has a more negative connotation than the first. Any ways for the authors to disentangle this difference?<br>- Table 2: Question 2 was only applicable to the participants who answered “yes” on question 1. The denominator should therefore be n=388. In addition, the counts do not add up to 388 (only 245), where the missings? Could patients include multiple answer options?<br>- Page 14, line 48: According to Table 1, 88% of the patients report that their disease was well controlled, but 20% of patients reported a much worse disease activity. How should this be interpreted, e.g. that patients report a much worse disease activity, but still have a controlled disease?<br>- A general comment is to avoid using subjective language in the results section ( “was lower in patients satisfied” or “reported fewer side effects”). Please support such statements numbers<br><br>Discussion<br>- One would expect the discussion to start with the main findings from this study. However, the authors have opted for starting with extensive information about the development of the biosimilar. Parts overlap with the introduction of the paper. What is the relevance of this information for the research questions? This section should be critically revised (or even removed) to reflect on the main findings from this study. This should include a discussion on if these align with what is already known about the topic, and supported with evidence from the field.<br>- The authors have included a statement on the “best outcomes” on page 18. This is quite vague. What are the best outcomes and for whom? From which perspective – patient, HCP, society?<br>- The authors should discuss the generalizability of their findings. Are these generalizable to the entire patient population; are the patient characteristics of those that participated in line with what is to be expected for the different indications. The study is performed |

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| | for one TNFalfa biosimilar, what about others (product related perceptions to be expected).<br>- The nocebo effect is included in the discussion. Do the authors think that the nocebo effect might have influenced their findings to some extend?<br>- The authors conclude with that we should learn from this study, including that we should good communication and shared decision making. This is something that has been echoed for a number of years but still does not seem to be implemented sufficiently or in a correct manner. The manuscript would benefit from a discussion or note on how the authors think this can be achieved.<br><br>Minor comments:<br>- Please add “OR” and “95% CI” to all the odds ratio’s presented.<br>- Page 19, line 46: Is there a . missing? Otherwise, please revise the long sentence<br>- It is not clear from the manuscript if any type of ethics assessment was performed for this study (or needed) |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Dr. Stanley Cohen, Metroplex Clinical Research Center Comments to the Author:
Interesting results from the survey which confirm previous observations in other population cohorts. Well written with clear presentation of the results

We would like to thank Dr. Cohen for his supportive review.

Reviewer: 2
Mrs. Helga Gardarsdottir, Utrecht University Utrecht Institute for Pharmaceutical Sciences Comments to the Author:
Thank you for the opportunity to review the manuscript entitled “The influence of information provided prior to switching from Humira to biosimilar adalimumab on UK patients’ satisfaction: a cross sectional survey by patient organisations.", which I read with great interest. The manuscript presents a well-conducted study with interesting results. However, I do have some comments on parts of the manuscript Major comments:

Introduction
Several statements in the introduction are not referenced or unclear, some examples include;
- Page 1, line 28-46 spendings on adalimumab. Please add reference to support your claims/theories

Thank you for this comment. We have added the reference as requested. https://pharmaceutical-journal.com/ article/feature/preparing-for-the-big-biologic-switch
- Page 8, line 52-53: reference to studies on perception of patients that have not switched, what are these? Would be useful to include to show relevance.

This issue has already been addressed in the existing text as follows: “Although some previous studies have investigated the knowledge and perception of biosimilars among patients who had not yet switched to biosimilars from originators4 5, the satisfaction and perception of the switching process among patients who have already experienced it remains unclear.” In order to further clarify

the contextual relevance of this, the last sentence of the introduction has been modified to read “The survey was conducted in the UK to investigate the perceptions and experiences of patients about the process of switching from Humira to biosimilar adalimumab after the switch had been made.”

- Page 9, line 6-9: The authors state that switching may cause anxiety and suspicion, please reference this statement.

Thank you for this comment. We have referenced the statement as requested. Bridges SL Jr, White DW, Worthing AB, et al. The Science Behind Biosimilars: Entering a New Era of Biologic Therapy. Arthritis Rheumatol. 2018;70(3):334-44. doi: 10.1002/art.40388. [published Online First: 2018/02/07].

Method

- The development of the survey is not described in any detail. What steps were taken during the development? How did the authors go about validating the questions asked?

Thank you for this comment. We have added the following detail to the methods section:
The survey was undertaken for the purposes of service evaluation, prompted by the statement in NHS England’s biosimilar commissioning framework that “shared decision making between clinical prescribers and patients will be vital if the best value, clinically effective medicines are to be used”. The data were collected and analysed anonymously in subjects following a switch from originator to biosimilar adalimumab. The survey questions were designed to investigate the patients’ experience of the switching process. Survey questions were developed by members of the patient organisations based upon issues determined to be of importance to patients. Face validity of the questions formulated was established by asking members of the relevant patient organisations to read through the questions and check them for sense and relevance.

- How did the authors analyse the comments and answers to the fully open questions reported?

Findings from the free comments were not analysed as a part of the present work and have not been presented here. This has been documented in the method section of the manuscript.

- When assessing participants perception on efficacy, the authors excluded all patients that reported “the same”. This is a major concern and seems strange as one would assume that switching to a similar product should not necessarily improve perception on efficacy, but to sustain or improve (at least not lead to worse perception). The results show that a large part of the population does opt for this answer, and it would also be expected.

The respondents that reported that the efficacy of the biosimilar was “the same” were not excluded from analysis as we report in the results section that “with respect to symptom control after the switch, 47% reported it to be the same”. As we explained in the text of the methods, “patients who answered “slightly better” and “much better” in questions 15 to 18 were assigned to a category of “better perception” and those who answered “slightly worse” and “much worse” were assigned to a category of “worse perception”. Those participants responding that the efficacy of the biosimilar was “the same” as originator or “not applicable (N/A)” were excluded from these categories” but not excluded from analysis.

Results

- Where are the results from the free comments and open questions presented? (see also my comment on the method section)

Findings from the free comments were not analysed as a part of the present work and have not been presented here. This has been documented in the method section of the manuscript.

- Information on if patients were satisfied with Humira before switching are missing. Was this measured? As the biosimilar is similar, patients who were not satisfied with Humira before switching might be less likely to feel satisfied with the biosimilar (Table 2, question 4).

Regarding satisfaction with Humira prior to the switch, only 2% of all respondents reported that their disease was either “not controlled” or “not well controlled at all” on Humira prior to switching (Table 1). Another 9% responded that their disease was “neither controlled well nor not controlled”. Therefore, it is unlikely that dissatisfaction with Humira prior to the survey will have greatly influenced the findings. Usual clinical practice would be to consider switch from an originator to a biosimilar in a subject judged by the physician as having achieved well-controlled disease activity. For a patient who perceives themselves as having a good response to Humira, it might be very daunting to hear that substitution of an alternative and less costly agent is being recommended. It was to investigate precisely this issue, and the influence of the manner in which a switch was communicated and undertaken, that this survey was proposed by the patient organisations and their patient representatives.

- On page 14, line 24-30 the results show that patients reported lack of training and majority reported that they did not receive an option to decline or delay switching to a biosimilar. Where these elements obligatory to offer based on the NHS recommendation? In addition, for some questions the answer can represent two types of views. Such as when it regards the option to decline - was the question asked if they wanted to switch? Or did they object to switching but this was not offered as an option? The latter has a more negative connotation than the first. Any ways for the authors to disentangle this difference?

It was not an obligatory requirement throughout the NHS to offer patients training or to present patients with an option to decline a request to switch from the originator to a biosimilar adalimumab. Participating patients were asked to complete the survey once they had completed the switching processes. This population did not, therefore, include any subjects who were given an option to switch or not, and chose not to switch. Those subjects reporting that they did not have an option to decline or delay the switch to biosimilar were not presented with the option to continue with the originator. This has been clarified in the text.

- Table 2: Question 2 was only applicable to the participants who answered “yes” on question 1. The denominator should therefore be n=388. In addition, the counts do not add up to 388 (only 245), where the missings? Could patients include multiple answer options?

Thank you for pointing out this error which was due to a line missing from Table 2. As you correctly point out, Question 2 was only applicable to the participants who answered “yes” on question 1. The missing line, which has now been completed, indicates that 139 patients responded in the form of free comments. There were four responses missing and this accounts for the total denominator of 388. As we have responded to your question above, the findings from the free comments were not analysed as a part of the present work and have not been presented here. This has been documented in the method section of the manuscript and has also been added as a footnote to Table 2.

- Page 14, line 48: According to Table 1, 88% of the patients report that their disease was well controlled, but 20% of patients reported a much worse disease activity. How should this be interpreted, e.g. that patients report a much worse disease activity, but still have a controlled disease?

We apologise for any confusion caused here. The Data in Table 1 which indicate that 88% of patients report that their disease was either “well controlled or very well controlled” referred to their self-

assessment prior to the switch to biosimilar. In order to clarify this, the text in the first section of the results has been amended to read “By self-evaluation of disease activity prior to switch, the majority (62%) were very well controlled, and 26% well controlled.” Furthermore, the relevant subheading in Table 1 has been amended to read “Patient-assessed disease activity prior to switch, n (%)” and the main heading has been amended to read “Participant baseline characteristics”.

- A general comment is to avoid using subjective language in the results section ( “was lower in patients satisfied” or “reported fewer side effects”). Please support such statements numbers

Thank you for this observation. We have added the relevant data to the text.

Discussion

- One would expect the discussion to start with the main findings from this study. However, the authors have opted for starting with extensive information about the development of the biosimilar. Parts overlap with the introduction of the paper. What is the relevance of this information for the research questions? This section should be critically revised (or even removed) to reflect on the main findings from this study. This should include a discussion on if these align with what is already known about the topic, and supported with evidence from the field.

Thank you for these suggestions. We have made extensive revisions to the discussion.

- The authors have included a statement on the “best outcomes” on page 18. This is quite vague. What are the best outcomes and for whom? From which perspective – patient, HCP, society?

Thank you for this comment. Our original statement was in reference to the patient perspective. To provide clarity, we have revised the discussion section as follows: “Our findings unequivocally highlight the importance of provision of clear, co-produced information about the switch to biosimilar as well as appropriate training in the use of a new injection device. The clear consequence of this best practice is a reduction in patient reported side effects and injection related pain as well as improved ease of using the injection device and reduction in any negative perceptions regarding symptom control with the new biosimilar.”

- The authors should discuss the generalizability of their findings. Are these generalizable to the entire patient population; are the patient characteristics of those that participated in line with what is to be expected for the different indications. The study is performed for one TNFalfa biosimilar, what about others (product related perceptions to be expected).

Thank you for this comment. The known patient characteristics are in line with those expected for the different indications. We have added the following text to the discussion: “It is thought likely that learnings regarding the importance of good communication and training will be generalizable to switching between other biologic originators and their biosimilars.”

- The nocebo effect is included in the discussion. Do the authors think that the nocebo effect might have influenced their findings to some extend?

Thank you for raising this important point. In the light of the survey findings, we think that it is very likely that the nocebo effect will have influenced findings. We have amended the discussion text to reflect this as follows: “So-called “nocebo” responses have been previously documented and may be augmented by poor communication around the switching process. It is likely that nocebo responses might account for some of the reported dissatisfaction with the biosimilar in this large sample of

survey respondents given that over a quarter were dissatisfied with either the verbal or written information communicated at the time of switch to adalimumab biosimilar."

- The authors conclude with that we should learn from this study, including that we should good communication and shared decision making. This is something that has been echoed for a number of years but still does not seem to be implemented sufficiently or in a correct manner. The manuscript would benefit from a discussion or note on how the authors think this can be achieved.

Thank you for this suggestion. We have added the following text to the discussion: "Means to facilitate this include preparation of clearly presented written material, produced with patient involvement, explaining the therapeutic and safety equivalence of biosimilars to their originators as well as the reasons that there are associated cost savings, and the benefits these might provide for the individual, the clinical service and to broader society. Furthermore, healthcare professionals involved in the switch process, including physicians, nurses, pharmacists, and others, would benefit from training in use of different injection devices, provision of key verbal information and reassurance, and how to respond to frequently asked questions."

Minor comments:
- Please add "OR" and "95% CI" to all the odds ratio's presented.
The text has been amended accordingly.

- Page 19, line 46: Is there a . missing? Otherwise, please revise the long sentence
Thank you for pointing out this error. The sentence has been revised as recommended.

- It is not clear from the manuscript if any type of ethics assessment was performed for this study (or needed) The purpose of this patient survey was for service evaluation which does not require ethics approval. We have made clear in the text that the patient survey was undertaken for the purposes of service evaluation and that data were collected and analysed anonymously.